Members of the Commission, it is a pleasure to have the opportunity to talk with you today about the challenges of implementing the federal standards for the protection of research subjects. I will be addressing this issue from my perspective as an IRB professional. In this role I spend most of my time working with researchers and IRBs to ensure that research is conducted according to the principles of the Belmont Report and in compliance with the applicable US regulations. In addition, I have spent a great deal of time over the last decade providing technical assistance to IRBs in low-resource settings at institutions collaborating in federally-funded research, and therefore expected to adhere to federal standards.

I would like to begin by taking you back in time to the late 1990s and early 2000s. In the 1990s the most prominent enforcer of the regulations governing IRBs was the NIH's Office of Protection from Research Risks, or OPRR. At that time, the Director of OPRR would frequently repeat a mantra that said "If it isn't documented, it didn't happen." This was always said in the context of talking about how detailed IRB records needed to be in order to achieve compliance with the OPRR interpretation of the regulations. In response IRB offices began to tighten up their operations.

At the same time, OPRR was in the midst of taking numerous actions against institutions that were determined to be out of compliance with the federal standards. These actions included suspending federally funded research, an action known as a shut down. In many instances, this was due to findings of administrative non-compliance, and subject safety was not an issue. This certainly got the attention of the IRB community and institutional leadership.

In 2000 OPRR was dissolved and a new office, the Office for Human Research Protections, or OHRP was established within the Department of Health and Human Services. At the time many believed that this was in part because of the heavy-handedness of OPRR, and there was hope that the change may lead to a more collegial relationship between the regulators and the implementers. So what, you may wonder, was the focus of the new regime? In a word, it was compliance. In presentations at the time of the rollout, OHRP's responsibilities included "implementation and interpretation of federal regulations and policy" and "evaluation of compliance." The new OHRP identified its overarching concerns in the form of questions like: *"Is there a 'culture of compliance'?"*; *"Are IRB members and investigators knowledgeable about* ***regulatory*** *requirements?"*; *"Is there adequate documentation of IRB findings and actions?"* Application of the ethical principles was absent from the discussion, and this regulatory-focused compliance approach set a tone that exists even today.

So, what was the result of this emphasis on regulatory compliance? The result was that the IRB community put itself of the compliance express. This was expressed in both good and bad ways. On the good side, the work of IRBs gained more recognition and there was a much-needed professionalization of the field. Leadership at research institutions had to sit up and take notice of the IRB – nobody wanted to be on the receiving end of a suspension. The idea of a comprehensive Human Research Protection Program gained traction, and there was a renewed emphasis on training in basic research ethics for IRB members and researchers. In addition, best practices in IRB management emerged and people in my line of work could now obtain credentials as certified IRB professionals. But there were problems when one peered over the top of his or her rose-colored glasses.

Obsessed with compliance, or with not being found non-compliant – IRBs cast a wider net, reviewing more activities than ever before. If it looked like research and quacked like research, it was going to the IRB. Better safe than sorry. Critics in the research community took notice, and decried the "mission creep" that was evident everywhere, especially in non-biomedical research. IRBs were now reviewing oral histories, journalism projects, student projects. This was especially difficult for the non-biomedical research community because IRB review meant compliance with regulations that were written primarily in response to ethical lapses in and for the regulation of biomedical research. While the regulations themselves offer a great deal of flexibility, particularly for research in the social sciences, many IRBs were afraid to take advantage of the flexibility because it required largely subjective decision-making on the part of IRBs, and there was an aversion to making a decision that might be questioned by the regulators.

Another by-product of the emphasis on compliance that affected how the federal standards were implemented was the emergence of accreditation for IRBs and HRPPs. While accreditation may be beneficial to some institutions and their HRPPs, there is concern that the accreditation standards disproportionately emphasize regulatory compliance over quality of ethics review, and that accreditation sets the bar far higher than what is actually required by the regulations.

Now that I have laid out the current context in which the federal standards are implemented I will talk specifically about challenges related to implementation.

The first challenge would be to determine what we mean by the federal standards. In general, when talking about the regulations we tend to lump them into two groups – the Common Rule regulations and the regulations for the Food and Drug Administration. The latter are fairly discrete and clear – research on an FDA-regulated drug or device will trigger requirements found under 21 CFR 50, 56, 312, 812 and others.

The Common Rule, on the other hand, is less so. While the basic Subpart A language of 45 CFR 46 have been commonly adopted by many federal departments or agencies, they are, in fact, separate regulations that emanate from different points of authority, and lack common understanding and enforcement. While we tend to think that OHRP has enforcement authority over the Common Rule the truth is that their jurisdiction is limited to research conducted or supported by Health and Human Services. In addition, Common Rule departments and agencies have not uniformly adopted subparts B through E.

So for example, under the current US Agency for International Development regulations – a Common Rule signatory – there are no additional regulatory protections for children, prisoners, or pregnant women – USAID has not adopted subparts B, C, or D. It is therefore possible that NIH and USAID could independently fund identical research involving these populations, and there would be drastically different regulatory requirements for each. Does this make one study more ethically sound than the other? This patchwork quilt of federal standards is confusing and difficult to implement for the institutions, investigators and IRBs seeking to comply.

In addition, there are U.S. departments and agencies that conduct research but are not signatories to the Common Rule, and research that is privately financed and does not involve an FDA-regulated product is not subject to any federal oversight or regulation – an

astonishing gap. My conclusion on this point is that applying the federal standards in the absence of a truly "common" rule is a challenge in and of itself.

Another area where implementing the federal standard presents a challenge to researchers and IRBs is the regulatory requirements for informed consent. Obtaining the voluntary informed consent of potential research subjects is a cornerstone protection. However, concerns about regulatory compliance, institutional liability, and other outside demands such as HIPAA and GINA have hijacked informed consent and replaced informed consent as a vehicle for protecting subjects with informed consent as a vehicle for protecting institutions. While it is true that there is inherent flexibility in the informed consent regulations, they are routinely abandoned by IRBs that are afraid of accidentally missing something or omitting that one bit of information that could be of importance to potential subjects. Too often, the default is to include everything.

The current federal standards are largely the same as they were 30 years ago. At that time the research environment was very much focused on the institution – hence the idea of the Institutional Review Board. The regulations did not anticipate the move to collaborative, multi-institutional research, nor has it evolved to keep up with the times. Rather than assess and revise the regulations, the system relies on interpretive guidance from regulators, and the emergence of the independent – or commercial – IRB system. However, even with this guidance and available alternative models of IRB review, many institutions insist on local IRB review and oversight even when they are one of perhaps dozens of IRBs reviewing a study, and even when the nature of multi-site research means that the protocol must be more or less accepted as-is. IRB review of a protocol by multiple IRBs is cumbersome, counter-productive, and without evidence showing that it provides greater protection of subjects.

Finally, I would like to speak for a few minutes about the challenges of implementing the federal standards in an international context. As is the case with multi-site research, the regulations did not anticipate international research. All of the challenges I have discussed are equally problematic – and at times more problematic – in the global context.

For example, foreign institutions who receive funding from HHS are required to apply for a Federalwide Assurance, or FWA. There is an international version of the FWA that provides foreign institutions the opportunity to identify which standards they will apply in the oversight and conduct of research. Several international standards are listed in addition to the US regulatory standards, implying that these non-US standards are suitable for research covered by a foreign institution's FWA. However, this is not the case, and in 2006 it was noted in the federal register that "For HHS-conducted or -supported research, all institutions holding an … FWA and engaged in such research must comply with the requirements of 45 CFR part 46." And "That *compliance is required regardless of whether the institution marked … other procedural standards* on the FWA form." As a result foreign institutions conducting HHS-funded research are expected to understand and apply the U.S. federal standards, including all current guidances, interpretations, and nuances even when there are highly regarded local standards and a robust research ethics infrastructure.

Applying the federal standards for informed consent – while taking into account the challenges I described previously – is also problematic in international research. On more

than one occasion I have sat in on meetings of international IRBs that wonder why they are being asked to approve the California Experimental Subject's Bill of Rights, or a HIPAA authorization form, or consent forms that advise subjects to report problems to individuals and institutions located half a world away.

While problems of this nature can be comical and often corrected administratively, there is a more serious problem when a 15 page consent form is required for use in a population with low literacy, or when a signature is insisted upon in settings where signing a piece of paper is usually the pre-cursor to bad things happening. There is something disingenuous about giving someone a copy of their multipage consent form after they have indicated their willingness to participate with a thumbprint because they are incapable of reading or writing. Again, a laser-like focus on demonstrating regulatory compliance trumps the common sense that I imagine the drafters of the Common Rule would have expected IRBs and institutions to apply.

So I will stop there and I look forward to discussing this issue with the commission.